

09/117,357

(FILE 'HOME' ENTERED AT 17:09:36 ON 20 MAY 2000)

L1 FILE 'INPADOC' ENTERED AT 17:13:22 ON 20 MAY 2000
1 S EP 897721/PN

FILE 'STNGUIDE' ENTERED AT 17:13:57 ON 20 MAY 2000

FILE 'INPADOC' ENTERED AT 17:14:09 ON 20 MAY 2000

FILE 'STNGUIDE' ENTERED AT 17:14:38 ON 20 MAY 2000

L2 FILE 'CAPLUS, USPATFULL' ENTERED AT 17:22:03 ON 20 MAY 2000
2483 S (LEUPRORELIN OR CETRORELIX OR BUSERELIN OR ANTIDE OR
RAMORELI
L3 804 S (RALOXIFEN# OR DROLOXIFEN OR CENTCHROMAN)
L4 17 S L2 AND L3
L5 17 DUP REM L4 (0 DUPLICATES REMOVED)
L6 1 S L5 AND GYNECOLOG?
L7 5 S L5 AND PY <=1997
L8 69 S LHRH(3A) (AGONIST# OR ANTAGONIST#) AND (ANTIESTROGEN# OR
ANTI(
L9 34 S L8 AND (GYNECOLOG? OR ENDOMETRIOS? OR MYOMA##)
L10 34 DUP REM L9 (0 DUPLICATES REMOVED)
L11 10 S L10 AND PY<=1996

FILE 'STNGUIDE' ENTERED AT 17:38:54 ON 20 MAY 2000

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09/117,357

FILE 'CAPLUS' ENTERED AT 17:22:03 ON 20 MAY 2000
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FILE 'USPATFULL' ENTERED AT 17:22:03 ON 20 MAY 2000
CA INDEXING COPYRIGHT (C) 2000 AMERICAN CHEMICAL SOCIETY (ACS)

=> s (leuprorelin or cetrorelix or buserelin or antide or ramorelix or zoladex or lhrh(3a) (agonist# or antagonist#))

L2 2483 (LEUPRORELIN OR CETRORELIX OR BUSERELIN OR ANTIDE OR RAMORELIX OR ZOLADEX OR LHRH(3A) (AGONIST# OR ANTAGONIST#))

=> s (raloxifen# or droloxifen or centchroman)

L3 804 (RALOXIFEN# OR DROLOXIFEN OR CENTCHROMAN)

=> s 12 and 13

L4 17 L2 AND L3

=> dup rem 14

PROCESSING COMPLETED FOR L4

L5 17 DUP REM L4 (0 DUPLICATES REMOVED)

=> s 15 and gynecolog?

L6 1 L5 AND GYNECOLOG?

=> d 16 abs ibib kwic 1

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2000 ACS

AB Combinations of LH-RH analogs and antiestrogens with tissue-selective estrogenic activity are useful for treatment of gynecol. disorders, esp. endometriosis and myomas. Thus, in rats with i.p. implants of endometrium

as a model of endometriosis, the LH-RH antagonist **antide** (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of endometriosis, but simultaneously to a redn. in endogenous estrogen level resembling that occurring after ovariectomy, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen **raloxifen** (3 mg/day orally) was also administered during the period of **antide** administration, the endometriosis regressed but no decrease in estrogen level occurred.

ACCESSION NUMBER: 1997:543582 CAPLUS

DOCUMENT NUMBER: 127:140580

TITLE: Combination of LH-RH analogs and antiestrogens for treatment of **gynecological** disorders

INVENTOR(S): Stoeckemann, Klaus; Muhn, Peter

PATENT ASSIGNEE(S): Schering A.-G., Germany

SOURCE: Ger. Offen., 5 pp.

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DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19604231	A1	19970731	DE 1996-19604231	19960129
WO 9727863	A1	19970807	WO 1997-EP395	19970129
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9715969	A1	19970822	AU 1997-15969	19970129
EP 877621	A1	19981118	EP 1997-902258	19970129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1209750	A	19990303	CN 1997-191940	19970129
BR 9707210	A	19990406	BR 1997-7210	19970129
JP 2000505422	T2	20000509	JP 1997-527295	19970129
NO 9803465	A	19980918	NO 1998-3465	19980728
PRIORITY APPLN. INFO.:				
DE 1996-19604231 19960129				
WO 1997-EP395 19970129				
TI	Combination of LH-RH analogs and antiestrogens for treatment of gynecological disorders			
AB	. . . esp. endometriosis and myomas. Thus, in rats with i.p. implants of endometrium as a model of endometriosis, the LH-RH antagonist antide (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of endometriosis, but simultaneously to. . . resembling that occurring after ovariectomy, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen raloxifene (3 mg/day orally) was also administered during the period of antide administration, the endometriosis regressed but no decrease in estrogen level occurred.			
ST	LHRH analog antiestrogen endometriosis treatment; antide raloxifene endometriosis treatment; myoma treatment LHRH analog antiestrogen; gynecol disorder LHRH analog antiestrogen			
IT	9034-40-6D, LHRH, analogs 31477-60-8, Centchroman 53714-56-0, Leuprorelin 57982-77-1 65807-02-5, Zoladex 82413-20-5, Droxifene 84449-90-1, Raloxifene 112568-12-4, Antide 120287-85-6, Cetrorelix 127932-90-5, Ramorelix 193147-32-9			
RL	BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (combination of LH-RH analogs and antiestrogens for treatment of gynecol. disorders)			

=> d his

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=> s 15 and py <=1997

L7 5 L5 AND PY <=1997

=> d 17 abs ibib kwic 1-5

L7 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2000 ACS

AB Combinations of LH-RH analogs and antiestrogens with tissue-selective estrogenic activity are useful for treatment of gynecol. disorders, esp. endometriosis and myomas. Thus, in rats with i.p. implants of endometrium

as a model of endometriosis, the LH-RH antagonist **antide** (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of

endometriosis, but simultaneously to a redn. in endogenous estrogen level resembling that occurring after ovariectomy, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen **raloxifene** (3 mg/day orally) was also administered during the period of **antide** administration, the endometriosis regressed but no decrease in estrogen level occurred.

ACCESSION NUMBER: 1997:543582 CAPLUS

DOCUMENT NUMBER: 127:140580

TITLE: Combination of LH-RH analogs and antiestrogens for treatment of gynecological disorders

INVENTOR(S): Stoeckemann, Klaus; Muhn, Peter

PATENT ASSIGNEE(S): Schering A.-G., Germany

SOURCE: Ger. Offen., 5 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

Appd.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19604231	A1	<u>19970731</u>	DE 1996-19604231	19960129 <--
WO 9727863	A1	<u>19970807</u>	WO 1997-EP395	19970129 <--
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9715969	A1	19970822	AU 1997-15969	19970129 <--
EP 877621	A1	19981118	EP 1997-902258	19970129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1209750	A	19990303	CN 1997-191940	19970129
BR 9707210	A	19990406	BR 1997-7210	19970129
JP 2000505422	T2	20000509	JP 1997-527295	19970129
NO 9803465	A	19980918	NO 1998-3465	19980728
PRIORITY APPLN. INFO.:			DE 1996-19604231	19960129
			WO 1997-EP395	19970129

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PI DE 19604231 A1 **19970731**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 19604231	A1	19970731	DE 1996-19604231	19960129 <--
WO 9727863	A1	19970807	WO 1997-EP395	19970129 <--
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9715969	A1	19970822	AU 1997-15969	19970129 <--
EP 877621	A1	19981118	EP 1997-902258	19970129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1209750	A	19990303	CN 1997-191940	19970129
BR 9707210	A	19990406	BR 1997-7210	19970129
JP 2000505422	T2	20000509	JP 1997-527295	19970129
NO 9803465	A	19980918	NO 1998-3465	19980728

AB . . . esp. endometriosis and myomas. Thus, in rats with i.p. implants. of endometrium as a model of endometriosis, the LH-RH antagonist **antide** (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of endometriosis, but simultaneously to. . . resembling that occurring after ovariectomy, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen **raloxifene** (3 mg/day orally) was also administered during the period of **antide** administration, the endometriosis regressed but no decrease in estrogen level occurred.

ST LHRH analog antiestrogen endometriosis treatment; **antide** **raloxifene** endometriosis treatment; myoma treatment LHRH analog antiestrogen; gynecol disorder LHRH analog antiestrogen

IT 9034-40-6D, LHRH, analogs 31477-60-8, **Centchroman**
53714-56-0, **Leuprorelin** 57982-77-1 65807-02-5,
Zoladex 82413-20-5, Droloxifene 84449-90-1, **Raloxifene**
112568-12-4, **Antide** 120287-85-6, **Cetrorelix**
127932-90-5, **Ramorelix** 193147-32-9

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (combination of LH-RH analogs and antiestrogens for treatment of gynecol. disorders)

L7 ANSWER 2 OF 5 USPATFULL

AB A method of inhibiting sexual precocity comprising administering to a human in need thereof an effective amount of a compound having the formula ##STR1## wherein R.¹ and R.³ are independently hydrogen,
--CH₂.³, ##STR2## wherein Ar is optionally substituted phenyl; R.² is selected from the group consisting of pyrrolidine, hexamethyleneamino, and piperidino; or a pharmaceutically acceptable salt of solvate thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 96:80284 USPATFULL
TITLE: Methods of Inhibiting sexual precocity
INVENTOR(S): Dodge, Jeffrey A., Indianapolis, IN, United States
PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5552417	19960903	<--
APPLICATION INFO.:	US 1995-442707	19950517 (8)	
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1993-171393, filed on 21		

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DOCUMENT TYPE: Utility
 PRIMARY EXAMINER: Fay, Zohreh
 LEGAL REPRESENTATIVE: Sales, James J.
 NUMBER OF CLAIMS: 5
 EXEMPLARY CLAIM: 1
 LINE COUNT: 394

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5552417 19960903

<--

SUMM Currently, three principal agents have been used to treat true precocious puberty including medroxyprogesterone acetate, cyproterone acetate, and **LHRH agonists**. The former two agents reverse or stop secondary sexual characteristics but do not effect height, particularly for girls. The . . . action of circulating estradiol on skeletal growth. Thus, these agents do not correct for the excessive amount of circulating estradiol. **LHRH agonists** are currently the therapy of choice for true precocious puberty and act to block the effects endogenous LHRH and functions.

DETD **Raloxifene**, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R.¹ and R.³ are hydrogen and R.² is 1-piperidinyl, is a nuclear regulatory molecule.

Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and . . . an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, **raloxifene** does block the action of estrogen in some cells; however in other cell types, **raloxifene** activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, **raloxifene** has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which **raloxifene** displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the **raloxifene**-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although **raloxifene** and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not. . . .

DETD . . . to effectively treat or prevent sexual precocity, or symptoms thereof, It also may be advantageous to administer a progestin or **LHRH agonist** with a compound of formula 1.

DETD Examples of specific capsule formulations of **raloxifene**, that have been made include those shown below:

DETD

Formulation 2: **Raloxifene** capsule
 Ingredient Quantity (mg/capsule)

Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD

Formulation 3: **Raloxifene** capsule
 Ingredient Quantity (mg/capsule)

Raloxifene

5

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Starch, NF 108
Starch flowable powder
225.3
Silicone fluid 350 centistokes
1.7

DETD
Formulation 4: **Raloxifene** capsule
Ingredient Quantity (mg/capsule)

Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD
Formulation 5: **Raloxifene** capsule
Ingredient Quantity (mg/capsule)

Raloxifene	50
Starch, NF	150
Starch flowable powder	
	397
Silicone fluid 350 centistokes	
	3.0

CLM What is claimed is:

5. The method of claim 1 wherein said human is also administered a progestin or **LHRH agonist**.

L7 ANSWER 3 OF 5 USPATFULL

AB A method of inhibiting fertility in women comprising administering to a female human an effective amount of a compound having the formula ##STR1## and pharmaceutically acceptable salts and solvates thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 95:97033 USPATFULL

TITLE: Methods of inhibiting fertility in women

INVENTOR(S): Jones, Charles D., Indianapolis, IN, United States

Tinsley, Frank C., Indianapolis, IN, United States

PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States
(U.S. corporation)

NUMBER DATE

PATENT INFORMATION: US 5462949 19951031
APPLICATION INFO.: US 1993-170945 19931221 (8)
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Fay, Zohreh
LEGAL REPRESENTATIVE: Sales, James J.; Dahling, Gerald V.
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
LINE COUNT: 385

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5462949 19951031

SUMM . . . stages of development are immunological methods (vaccination) and methods involving the direct control of LHRH secretion from the pituitary by LHRH agonists or antagonists.

SUMM . . . women. The methods of treatment provided by this invention are practiced by administering to a female human a dose of **raloxifene** or a pharmaceutically acceptable salt or solvate

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thereof, that is effective to inhibit fertility. The term inhibit fertility includes reducing. . .

SUMM **Raloxifene**, which is the hydrochloride salt of the compound of formula 1, has been shown to bind to the estrogen receptor. . . an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, **raloxifene** does block the action of estrogen in some cells; however in other cell types, **raloxifene** activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. The unique profile which **raloxifene** displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various

gene functions by the **raloxifene**-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although **raloxifene** and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not. . .

SUMM

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
------------	-----------------------

Raloxifene	0.1-1000
Starch, NF	0-650
Starch flowable powder	0-650
Silicone fluid 350 centistokes	0-15

DETD

Formulation 2: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
------------	-----------------------

Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD

Formulation 3: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
------------	-----------------------

Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD

Formulation 4: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
------------	-----------------------

Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

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DETD

Formulation 5: **Raloxifene** capsule
Ingredient Quantity (mg/capsule)

Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	
	3.0

DETD

Formulation 6: Tablets
Ingredient Quantity (mg/tablet)

Raloxifene	0.1-1000
Cellulose, microcrystalline	
	0-650
Silicon dioxide, fumed	
	0-650
Stearate acid	0-15

DETD

Formulation 7: Tablets
Ingredient Quantity (mg/tablet)

Raloxifene	0.1-1000
Starch	45
Cellulose, microcrystalline	
	35
Polyvinylpyrrolidone	
	4
(as 10% solution in water)	
Sodium carboxymethyl cellulose	
	4.5
Magnesium stearate	0.5
Talc	1

DETD

Formulation 8: Suspensions

Ingredient Quantity (mg/5 ml)

Raloxifene	0.1-1000	mg
Sodium carboxymethyl cellulose		
	50	mg
Syrup	1.25	mg
Benzoic acid solution		
	0.10	mL
Flavor	q.v.	
Color	q.v.	
Purified water to	5	mL

DETD . . . of the groups serves as the control group and the other groups as experimental groups, each such experimental group receiving **raloxifene** at a particular dose level. **Raloxifene** is prepared in corn oil such that the daily administration is in 0.1 ml. of vehicle. The designated quantity of **raloxifene** in the vehicle is administered to each rat within the defined group subcutaneously (sc) daily. Alternatively, administration may be made. . . . gavage or an intramuscular route. The control group receives only the vehicle. Administration of the vehicle or the combination of **raloxifene**

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and vehicle is continued on a daily basis for 15 days. On the 5th day of treatment, one or two. . . .
DETD The male rats are removed, and the experimental groups of female rats are administered **raloxifene** via oral garage, an intramuscular route, or by subcutaneous injection. The administration continues on a daily basis until the twelfth. . . .

L7 ANSWER 4 OF 5 USPATFULL

AB A method of inhibiting sexual precocity comprising administering to a human in need thereof an effective amount of a compound having the formula ##STR1## wherein R.sup.1 and R.sup.3 are independently hydrogen,
--CH.sub.3, ##STR2## wherein Ar is optionally substituted phenyl; R.sup.2 is selected from the group consisting of pyrrolidine, hexamethyleneamino, and piperidino; or a pharmaceutically acceptable salt of solvate thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 95:84387 USPATFULL
TITLE: Methods of inhibiting sexual precocity
INVENTOR(S): Dodge, Jeffrey A., Indianapolis, IN, United States
PATENT ASSIGNEE(S): Eli Lilly & Co., Indianapolis, IN, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5451590	19950919	<--
APPLICATION INFO.:	US 1993-171393	19931221 (8)	
DOCUMENT TYPE:	Utility		✓
PRIMARY EXAMINER:	Fay, Zohreh		
LEGAL REPRESENTATIVE:	Sales, James J.; Dahling, Gerald V.		
NUMBER OF CLAIMS:	5		
EXEMPLARY CLAIM:	1		
LINE COUNT:	383		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5451590 19950919 <--

SUMM Currently, three principal agents have been used to treat true precocious puberty including medroxyprogesterone acetate, cyproterone acetate, and **LHRH agonists**. The former two agents reverse or stop secondary sexual characteristics but do not effect final height, particularly for girls. The. . . . action of circulating estradiol on skeletal growth. Thus, these agents do not correct for the excessive amount of circulating estradiol. **LHRH agonists** are currently the therapy of choice for true precocious puberty and act to block the effects endogenous LHRH and functions. . . .

DETD **Raloxifene**, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R.sup.1 and R.sup.3 are hydrogen and R.sup.2 is 1-piperidinyl, is a nuclear regulatory molecule.

Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and. . . . an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, **raloxifene** does block the action of estrogen in some cells; however in other cell types, **raloxifene** activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, **raloxifene** has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which **raloxifene** displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the

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raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although **raloxifene** and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not. . . .
DETD . . . to effectively treat or prevent sexual precocity, or symptoms thereof. It also may be advantageous to administer a progestin or **LHRH agonist** with a compound of formula 1.
DETD Examples of specific capsule formulations of **raloxifene**, that have been made include those shown below:

DETD

Ingredient	Quantity (mg/capsule)
------------	-----------------------

Formulation 2: **Raloxifene** capsule

Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3: **Raloxifene** capsule

Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4: **Raloxifene** capsule

Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 5: **Raloxifene** capsule

Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

CLM What is claimed is:

5. The method of claim 1 wherein said human is also administered a progestin or **LHRH agonist**.

L7 ANSWER 5 OF 5 USPATFULL

AB A method of inhibiting ovarian dysgenesis, delayed puberty, or sexual infantilism comprising administering to a human in need thereof an effective amount of a compound having the formula ##STR1## wherein R.¹ and R.³ are independently hydrogen, --CH.₂Ar, ##STR2## wherein Ar is optionally substituted phenyl; R.² is selected from the group consisting of pyrrolidine, hexamethyleneamino, and piperidino; or a pharmaceutically acceptable salt of solvate thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 95:84386 USPATFULL

TITLE: Methods of inhibiting ovarian dysgenesis, delayed puberty, or sexual infantilism

INVENTOR(S): Dodge, Jeffrey A., Indianapolis, IN, United States

Delacroix

PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States
(U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5451589	19950919	<--
APPLICATION INFO.:	US 1993-170946	19931221 (8)	
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Fay, Zohreh		
LEGAL REPRESENTATIVE:	Sales, James J.; Dahling, Gerald V.		
NUMBER OF CLAIMS:	5		
EXEMPLARY CLAIM:	1		
LINE COUNT:	385		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			
PI	US 5451589	19950919	<--
DETD	Raloxifene , a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R. ^{sup.1} and R. ^{sup.3} are hydrogen and R. ^{sup.2} is 1-piperidinyl, is a nuclear regulatory molecule.		
Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and . . . an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, raloxifene does block the action of estrogen in some cells; however in other cell types, raloxifene activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, raloxifene has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which raloxifene displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the raloxifene -estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although raloxifene and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not. or sexual infantilism, or symptoms thereof. Also, other active ingredients may be administered to a human in need, such as LHRH agonists or progestins.			
DETD	Examples of specific capsule formulations of raloxifene , that have been made include those shown below:		
DETD	Ingredient	Quantity (mg/capsule)	
Formulation 2: Raloxifene capsule			
	Raloxifene	1	
	Starch, NF	112	
	Starch flowable powder	225.3	
	Silicone fluid 350 centistokes	1.7	
Formulation 3: Raloxifene capsule			
	Raloxifene	5	
	Starch, NF	108	
	Starch flowable powder	225.3	
	Silicone fluid 350 centistokes	1.7	
Formulation 4: Raloxifene capsule			
	Raloxifene	10	
	Starch, NF	103	
	Starch flowable powder		

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225.3
Silicone fluid 350 centistokes
1.7
Formulation 5: **Raloxifene** capsule
Raloxifene 50
Starch, NF 150
Starch flowable powder
397
Silicone fluid 350 centistokes
3.0

=> s lhrh(3a) (agonist# or antagonist#) and (antiestrogen# or anti(w)estrogen# or anti-oestrogen# or antioestrogen#)

UNMATCHED RIGHT PARENTHESIS 'TAGONIST#)) AND'
The number of right parentheses in a query must be equal to the number of left parentheses.

=> s lhrh(3a) (agonist# or antagonist#) and (antiestrogen# or anti(w)estrogen# or anti-oestrogen# or antioestrogen#)

L8 69 LHRH(3A) (AGONIST# OR ANTAGONIST#) AND (ANTIESTROGEN# OR ANTI(W)ESTROGEN# OR ANTI-OESTROGEN# OR ANTIOESTROGEN#)

=> s 18 and (gynecolog? or endometrios? or myoma##)

L9 34 L8 AND (GYNECOLOG? OR ENDOMETRIOS? OR MYOMA##)

=> dup rem 19

PROCESSING COMPLETED FOR L9

L10 34 DUP REM L9 (0 DUPLICATES REMOVED)

=> s 110 and py<=1996

L11 10 L10 AND PY<=1996

=> d 111 abs ibib kwic 1-10

L11 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2000 ACS

AB Since uterine leiomyomata (fibroids) are not found in conditions where estradiol is either absent or present only in low concns., estradiol is considered to be an important factor in the control of fibroid growth.

To detn. whether this is due to a direct effect on the tissue, estradiol and progesterone receptors were measured in tissue removed at hysterectomy from normally cycling women, women who had received the gonadotropin-releasing hormone (GnRH) agonist Zoladex (ICI 118630) as a s.c. depot given at monthly intervals for 3 mo preoperatively, and women who had received the **antiestrogen** tamoxifen (20 mg daily) for 3 mo before surgery. Both unoccupied estradiol receptors (measured by

sepg. bound from free hormone with dextran-coated charcoal) and total receptor populations (as measured by an enzyme immunoassay) were measured in each fibroid and adjoining myometrium. There was more binding of both estradiol and progestogen to fibroid than to myometrium in both the control and agonist-treated groups. Estradiol binding to fibroids in women treated with Zoladex exceeded that in the normally cycling women which in turn exceeded that in the tamoxifen-treated group. However, the binding of progestogen, measured by dextran-coated charcoal, showed the

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reverse trend. These results may be explained by the low circulating estradiol concn. in the GnRH agonist-treated women, leading to low receptor occupancy.

ACCESSION NUMBER: 1989:206008 CAPLUS
DOCUMENT NUMBER: 110:206008
TITLE: The binding of steroids to myometrium and leiomyomata (fibroids) in women treated with the gonadotropin-releasing hormone agonist Zoladex (ICI 118630)
AUTHOR(S): Lumsden, M. A.; West, C. P.; Hawkins, R. A.; Bramley, T. A.; Rumgay, L.; Baird, D. T.
CORPORATE SOURCE: Cent. Reprod. Biol., Univ. Edinburgh, Edinburgh, EH3 9EW, UK
SOURCE: J. Endocrinol. (1989), 121(2), 389-96
CODEN: JOENAK; ISSN: 0022-0795
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Endocrinol. (1989), 121(2), 389-96
CODEN: JOENAK; ISSN: 0022-0795
AB . . . (ICI 118630) as a s.c. depot given at monthly intervals for 3 mo preoperatively, and women who had received the **antiestrogen** tamoxifen (20 mg daily) for 3 mo before surgery.. Both unoccupied estradiol receptors (measured by sepg. bound from free hormone. . .
ST leiomyomata steroid receptor; **LHRH agonist** uterus steroid receptor
IT **Myoma**
(leio-, estradiol and progestogen receptors of, in women, gonadotropin-releasing hormone agonist effect on)

L11 ANSWER 2 OF 10 USPATFULL

AB Certain steroidal and non-steroidal compounds have been found to inhibit androgen and estrogen formation. Such inhibition may aid in the reduction of the activity of these hormones and may be useful in the treatment of diseases where, for example, inhibition of androgen or estrogen activity is desired. Preferred inhibitors also possess antiestrogenic activity, thus providing the advantage of a double inhibitory action both on estrogen formation and on estrogen action (blockade of estrogen receptors by antiestrogenic action).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 96:116412 USPATFULL
TITLE: Inhibitors of sex steroid biosynthesis and methods for their production and use
INVENTOR(S): Labrie, Fernand, Ste.-Foy, Canada
Merand, Yves, Ste.-Foy, Canada
PATENT ASSIGNEE(S): Endorecherche Inc., Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5585405	19961217	<--
APPLICATION INFO.:	US 1994-283989	19940801 (8)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1992-966112, filed on 22 Oct 1992, now patented, Pat. No. US 5364847 which is a continuation of Ser. No. US 1989-322154, filed on 10 Mar 1989, now abandoned		
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Jordan, Kimberly		
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen, LLP		
NUMBER OF CLAIMS:	7		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	3 Drawing Figure(s); 3 Drawing Page(s)		
LINE COUNT:	1357		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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PI US 5585405 19961217 <--
 DETD . . . sex steroid formation and to act as antagonists to sex steroid activity by blocking sex steroid receptors. For example, preferred **antiestrogens** which also act as inhibitors of estrogen formation include, but are not limited to, N-butyl,
 N-methyl-11-(16.alpha.-chloro-
 3', 17'.beta.-dihydroxy estra-1',3',5'(10')-trien-7'.alpha.-yl) undecanamide ("EM. . . are not limited to, malignant as well as non-malignant steroid-sensitive diseases, especially breast cancer, prostate cancer, ovarian cancer, endometrial cancer, **endometriosis**, uterine leiomyomata, precocious puberty, hirsutism, acne, seborrhea, androgenic alopecia benign prostatic hyperplasia, sexual deviants as well as for male and. . . at a step preceding steroid receptors, thus acting prior to and in addition to the action of steroid antagonists (e.g. **antiestrogens** or antiandrogens).
 DETD Such compounds administered at appropriate doses are of value in all conditions where **antiestrogens** and antiandrogens are beneficial. In particular this approach is of value in breast cancer, prostate cancer, endometrial cancer, ovarian cancer, **endometriosis**, benign prostatic hyperplasia, precocious puberty, hirsutism, acne, seborrhea, androgenic alopecia, menstrual disorders and as male and female contraceptive as well. . . .
 DETD . . . dosage of the above-described compound (multi sex hormone blocker) are the same as in intact patients or patients receiving an **LHRH agonist or antagonist**.
 DETD The composition may contain, in addition to the steroid and/or nonsteroidal derivatives of the invention, other **antiestrogens** and/or antiandrogens and/or enzymatic inhibitors and/or inhibitors of ACTH and/or growth hormone and/or prolactin secretion.
 DETD . . . phase was washed with water, dried on anhydrous Na.₂SO₄ and evaporated under reduced pressure. The residue included two important **antiestrogens** which were separated by chromatography on silica gel and eluted with a mixture of EtOAc/hexane (4:6 v/v) to give: N-butyl, . . .

L11 ANSWER 3 OF 10 USPATFULL

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 96:97032 USPATFULL
 TITLE: Methods for preventing and treating osteoporosis with low dose non-masculinizing androgenic compounds
 INVENTOR(S): Labrie, Fernand, Quebec, Canada
 PATENT ASSIGNEE(S): Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5567695	19961022	<--
APPLICATION INFO.:	US 1995-483761	19950607 (8)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-282964, filed on 29 Jul 1994 which is a division of Ser. No. US 1993-15083, filed on 8 Feb 1993, now patented, Pat. No. US 5362720 which is a continuation of Ser. No. US 1991-724532,		

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filed on 28 Jun 1991, now abandoned

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Nutter, Nathan M.
LEGAL REPRESENTATIVE: Ostrolenk, Faber, Gerb & Soffen, LLP
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1453
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5567695 19961022

<--

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and. . .

SUMM This invention relates to a method for treating or preventing breast and

endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to kits containing active ingredients. . .

SUMM . . . for breast and endometrial cancer as well as for the prevention

and treatment of bone loss and for treatment of **endometriosis**. The main approaches for the treatment of already developed breast cancer

are related to the inhibition of estrogen action and/or. . .

SUMM . . . irradiation, two procedures giving irreversible castration.

Recently, a reversible form of castration has been achieved by utilizing

Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum estrogens to castrated levels. . .

SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20:1381, 1984; Manni et al., Endocr. Rev. 7:89-94, 1986). Beneficial effects of treatment with **LHRH agonists** have also been observed in postmenopausal women (Nicholson et al., J. Steroid Biochem. 23:843-848, 1985).

SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.

SUMM . . . relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an **antiestrogen** to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.

SUMM . . . No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which includes various specified combinations of compounds selected from **LHRH agonists**, antiandrogens, **antiestrogens** and certain inhibitors of sex steroid biosynthesis.

SUMM . . . 4,472,382 relates to treatment of prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors with specified pharmaceuticals or combinations. Various **LHRH agonists** and antiandrogens are discussed.

SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.

SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means

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(use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10] **LHRH** ethylamide, or **antagonists**) as part of a combination therapy.

Antiestrogens, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . .

SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa.. . .

SUMM . . . ZR-75-1 human breast carcinoma cells is inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo. . . .

SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

SUMM . . . 40% in unselected breast cancer patients (Horwitz, J. Steroid Biochem. 27:447-457, 1987), an efficacy comparable to that of the non-steroidal **antiestrogen** tamoxifen (Lippman, Semin. Oncol. 10 (Suppl.): 11-19, 1983). Its more general use, however, is for breast cancer relapsing after other. . . .

SUMM The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50:743, 1987; Preston, Obstet, Gynecol. 2:152, 1965). Androgenic and masculinizing side effects (sometimes irreversible) are however. . . .

SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . of said androgenic steroid described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for all purposes which are enhanced by administering androgens or otherwise. . . .

DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . . .

DETD . . . prevent other signs and symptoms of menopause. In women, when estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . . .

DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . . .

DETD . . . the above therapy using the described regimen, tumor growth of

breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 4 OF 10 USPATFULL

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose. Of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 96:72882 USPATFULL
TITLE: Activation of androgen receptors with low dose non-masculinizing androgenic compounds
INVENTOR(S): Labrie, Fernand, Quebec, Canada
PATENT ASSIGNEE(S): Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5545634	19960813	<--
APPLICATION INFO.:	US 1994-282964	19940729 (8)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1993-15083, filed on 8 Feb 1993, now patented, Pat. No. US 5362720 which is a continuation of Ser. No. US 1991-724532, filed on 28 Jun 1991, now abandoned		
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Nutter, Nathan M.		
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen, LLP		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	1406		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			
PI	US 5545634	19960813	<--
AB	A method of treatment or prevention of breast and endometrial cancer, osteoporosis and endometriosis in susceptible warm-blooded animals comprising administering a low dose. Of a progestin or other steroid derivative having androgenic activity and. . .		
SUMM	This invention relates to a method for treating or preventing breast and endometrial cancer, bone loss, and for treating endometriosis in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to kits containing active ingredients. . .		
SUMM	. . . for breast and endometrial cancer as well as for the prevention and treatment of bone loss and for treatment of endometriosis . The main approaches for the treatment of already developed breast cancer are related to the inhibition of estrogen action and/or. . .		
SUMM	. . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing Luteinizing Hormone-Releasing Hormone Agonists (LHRH agonists) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum		

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estrogens to castrated levels. . . .

SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20: 1381, 1984; Manni et al., Endocr. Rev. 7: 89,-94, 1986). Beneficial effects of treatment with **LHRH agonists** have also been observed in postmenopausal women (Nicholson et al., J. Steroid Biochem. 23: 843-848, 1985).

SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.

SUMM . . . relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an **antiestrogen** to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.

SUMM . . . No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which includes various specified combinations of compounds selected from **LHRH agonists**, antiandrogens, **antiestrogens** and certain inhibitors of sex steroid biosynthesis.

SUMM . . . 4,472,382 relates to treatment of prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors with specified pharmaceuticals or combinations. Various **LHRH agonists** and antiandrogens are discussed.

SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.

SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means (use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]**LHRH** ethylamide, or antagonists) as part of a combination therapy.

Antiestrogens, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . . .

SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa. . . .

SUMM . . . ZR-75-1 human breast carcinoma cells is inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo. . . .

SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

SUMM . . . in unselected breast cancer patients (Horwitz, J. Steroid Biochem. 27: 447-457, 1987), an efficacy comparable to that of the non-steroidal **antiestrogen** tamoxifen (Lippman, Semin. Oncol. 10 (Suppl.): 11-19, 1983). Its more general use, however, is for breast cancer relapsing after other. . . .

SUMM The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet, Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . . .

SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects

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on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . of said androgenic steroid described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for all purposes which are enhanced by administering androgens or otherwise.

DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . .

DETD . . . prevent other signs and symptoms of menopause. In women, when estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . .

DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . .

DETD . . . the above therapy using the described regimen, tumor growth of breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 5 OF 10 USPATFULL

AB Methods of treatment and prevention of estrogen-related diseases, and of

fertility control, include low dose (e.g. less than 50 nanomolar serum concentration) administration of certain anabolic steroids, progestins and other substantially non-masculinizing androgenic compounds. Sustained release formulations substantially free of organic solvent, and sustained release formulations for maintaining low serum levels of androgen are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 96:67992 USPATFULL
TITLE: Controlled release systems and low dose androgens
INVENTOR(S): Labrie, Fernand, Quebec, Canada
PATENT ASSIGNEE(S): Lepage, Martin, Quebec, Canada
Endorecherche, Inc., Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5541172	19960730	<--
APPLICATION INFO.:	US 1995-474347	19950607 (8)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-398096, filed on 3 Mar 1995 which is a division of Ser. No. US 1992-900817, filed on 24 Jun 1992 which is a continuation-in-part of Ser. No. US 1991-724532, filed on 28 Jun 1991		
DOCUMENT TYPE:	Utility		

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PRIMARY EXAMINER: Nutter, Nathan M.
LEGAL REPRESENTATIVE: Ostrolenk, Faber, Gerb & Soffen
NUMBER OF CLAIMS: 1
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 2236
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5541172 19960730
SUMM This invention relates to a method for treating or preventing breast and
kits endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to containing active ingredients. . .
SUMM . . . for breast and endometrial cancer as well as for the prevention and treatment of bone loss and for treatment of **endometriosis**.
The main approaches for the treatment of already developed breast cancer are related to the inhibition of estrogen action and/or. . .
SUMM . . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing
Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum estrogens to castrated levels. . .
SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20: 1381, 1984; . . .
SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.
SUMM . . . relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an **antiestrogen** to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.
SUMM . . . No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which includes various specified combinations of compounds selected from **LHRH agonists**, antiandrogens, **antiestrogens** and certain inhibitors of sex steroid biosynthesis.
SUMM . . . 4,472,382 relates to treatment of prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors with specified pharmaceuticals or combinations. Various **LHRH agonists** and antiandrogens are discussed.
SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.
SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means (use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10] **LHRH** ethylamide, or **antagonists**) as part of a combination therapy.
Antiestrogens, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . .
SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did

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not respond to Tamoxifen could respond to Fluoxymesterone and vice versa. . . .

SUMM . . . ZR-75-1 human breast carcinoma cells is inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo. . . .

SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

SUMM . . . in unselected breast cancer patients (Horwitz, J. Steroid Biochem. 27: 447-457, 1987), an efficacy comparable to that of the non-steroidal **antiestrogen** tamoxifen (Lippman, Semin. Oncol. 10 (Suppl.): 11-19, 1983). Its more general use, however, is for breast cancer relapsing after other. . . .

SUMM . . . et al., Am. J. Obstet. Gynecol. 158: 797-807, 1988). The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet. Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . . .

SUMM The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet. Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . . .

SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . activities induced by estrogens. For example, estrogen-related diseases include but are not limited to breast cancer, endometrial cancer, bone loss, **endometriosis** and osteoporosis.

SUMM The methods described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for other purposes which are enhanced by administering androgens or otherwise. . . .

SUMM . . . for treating or preventing estrogen sensitive diseases and disorders including but not limited to breast cancer, endometrial cancer, osteoporosis and **endometriosis**. The methods comprise administering to a patient in need of such treatment or prevention, an effective amount of sustained release. . . .

DETD . . . not only for their more rational use in the prevention and therapy of breast and endometrial cancers as well as **endometriosis** and bone loss but also to avoid side effects caused by interaction with steroid receptors unnecessary for the desired beneficial. . . .

DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . . .

DETD . . . prevent other signs and symptoms of menopause. In women, when

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estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . .

DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . .

DETD . . . the above therapy using the described regimen, tumor growth of breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 6 OF 10 USPATFULL

AB Methods of treatment and prevention of estrogen-related diseases, and of

fertility control, include low dose (e.g. less than 50 nanomolar serum concentration) administration of certain anabolic steroids, progestins and other substantially non-masculinizing androgenic compounds. Sustained release formulations substantially free of organic solvent, and sustained release formulations for maintaining low serum levels of androgen are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 95:64916 USPATFULL

TITLE: Controlled release systems and low dose androgens

INVENTOR(S): Labrie, Fernand, Quebec, Canada

Lepage, Martin, Quebec, Canada

PATENT ASSIGNEE(S): Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5434146	19950718	<--
APPLICATION INFO.:	US 1992-900817	19920624 (7)	
DISCLAIMER DATE:	20111108		
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1991-724532, filed on 28 Jun 1991, now abandoned		
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Nutter, Nathan M.		
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen		
NUMBER OF CLAIMS:	16		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	15 Drawing Figure(s); 9 Drawing Page(s)		
LINE COUNT:	2424		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5434146 19950718 <--

SUMM This invention relates to a method for treating or preventing breast and

endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to

kits containing active ingredients. . .

SUMM . . . for breast and endometrial cancer as well as for the prevention

and treatment of bone loss and for treatment of **endometriosis**. The main approaches for the treatment of already breast cancer are related to the inhibition of estrogen action and/or formation. . .

SUMM . . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing

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Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum estrogens to castrated levels. . .

SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20: 1381, 1984; Manni et al., Endocr. Rev. 7: 89-94, 1986). Beneficial effects of treatment with **LHRH agonists** have also been observed in postmenopausal women (Nicholson et al., J. Steroid Biochem. 23: 843-848, 1985).

SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.

SUMM . . . relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an **antiestrogen** to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.

SUMM . . . No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which includes various specified combinations of compounds selected from **LHRH agonists**, antiandrogens, **antiestrogens** and certain inhibitors of sex steroid biosynthesis.

SUMM . . . 4,472,382 relates to treatment of prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors with specified pharmaceuticals or combinations. Various **LHRH agonists** and antiandrogens are discussed.

SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.

SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means (use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10] **LHRH** ethylamide, or **antagonists**) as part of a combination therapy.

Antiestrogens, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . .

SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa. . .

SUMM . . . ZR-75-1 human breast carcinoma cells in inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo. . .

SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

SUMM . . . in unselected breast cancer patients (Horwitz, J. Steroid Biochem. 27: 447-457, 1987), an efficacy comparable to that of the non-steroidal **antiestrogen** tamoxifen (Lippman, Semin. Oncol. 10 (Suppl.): 11-19, 1983). Its more general use, however, is for breast cancer relapsing after other. . .

SUMM . . . et al., Am. J. Obstet. Gynecol. 158: 797-807, 1988). The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet. Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . .

SUMM The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet. Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . .

SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . activities induced by estrogens. For example, estrogen-related diseases include but are not limited to breast cancer, endometrial cancer, bone loss, **endometriosis** and osteoporosis.

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SUMM . . . for treating or preventing estrogen sensitive diseases and disorders including but not limited to breast cancer, endometrial cancer, osteoporosis and **endometriosis**. The methods comprise administering to a patient in need of such treatment or prevention, an effective amount of sustained release. . .

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DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . .

DETD . . . prevent other signs and symptoms of menopause. In women, when estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . .

DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . .

DETD . . . the above therapy using the described regimen, tumor growth of breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 7 OF 10 USPATFULL

AB Inhibitors of sex steroid activity, for example those having the general structure ##STR1## may be used as part of a pharmaceutical composition to provide antiestrogenic effects and/or to suppress estrogen synthesis.

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Such pharmaceutical compositions are useful for the treatment of breast cancer or other diseases whose progress is aided by activation of sex steroid receptors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 95:20734 USPATFULL
TITLE: Anti-estrogenic compounds and compositions
INVENTOR(S): Labrie, Fernand, Quebec, Canada
Merand, Yves, Quebec, Canada
PATENT ASSIGNEE(S): Endorecherche Inc., Canada (non-U.S. corporation)

NUMBER	DATE
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PATENT INFORMATION:	US 5395842 19950307	<--
APPLICATION INFO.:	US 1991-801704 19911202 (7)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1988-265150, filed on 31 Oct 1988, now abandoned And a continuation-in-part of Ser. No. US 1989-377010, filed on 7 Jul 1989, now abandoned	

DOCUMENT TYPE:	Utility
PRIMARY EXAMINER:	Cintins, Marianne M.
ASSISTANT EXAMINER:	Criares, T. J.
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen
NUMBER OF CLAIMS:	66
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT:	3525

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI	US 5395842 19950307	<--
SUMM	This invention relates to novel inhibitors of sex steroid activity such as antiestrogen compounds having effective antagonistic capability while substantially lacking agonistic effects. More particularly, certain preferred embodiments of the invention relate to. . . . the amount of sex steroid available to act at these sites. For example, alternative or concurrent therapy to administration of antiestrogens could involve attempts to block the production of estrogens (e.g. by ovariectomy) such that less is available to activate receptor. . . .	
SUMM	There is, therefore, a need in the art for antiestrogens which effectively block estrogen receptors with minimal or no agonistic effect. In Wakeling and Bowler, "Steroidal Pure Antioestrogens ", J. Endocrinol. 112:R7-R10 (1987), a steroid derivative is said to act as an antiestrogen but to exhibit some estrogen activity. The net effectiveness of a compound is effected by both its agonistic (undesirable) and. . . .	
SUMM	In U.S. Pat. No. 4,094,994, it is disclosed that the use of certain antiestrogens may inhibit certain human breast tumor cells.	
SUMM	H. Mouridsen et al., Cancer Treatm. Rev. 5: 131-141 (1978), discloses that Tamoxifen, an antiestrogen , is effective in remission of advanced breast cancer in about 30 percent of the women patients treated.	
SUMM	The combined use of the antiestrogen Tamoxifen and a luteinizing hormone-releasing hormone agonist, Buserelin, is also known for treatment of breast cancer. See, for instance, Klijn. . . .	
SUMM	. . . male animals including humans whose testicular hormonal secretions are blocked by surgical or chemical means, e.g., by use of an LHRH agonist , e.g., [D-Trp.sup.6, des-Gly-NH.sup.2.sup.10]LHRH ethylamide. The treatment includes administering an antiandrogen, e.g., flutamide in association with at least one inhibitor. . . .	
SUMM	U.S. Pat. No. 4,472,382 relates to a method of treating prostate cancer	

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using the combination of an antiandrogen and an **LHRH** agonist.

SUMM Von Angerer et al. discuss other **antiestrogens** in "1-(aminoalkyl)-2-phenylindoles as Novel Pure Estrogen Antagonists", J. Med. Chem. 1990; 33: 2635-2640. In U.S. Pat. No. 4,094,994, where it is said that the use of certain **antiestrogens** inhibit certain human breast tumor cells. See also DE 3821148.

SUMM . . . et al., J. Med. Chem. 33: 3216-3222 and 3222-3229 (1990) described the synthesis and biological activities of 2,3-diaryl-2H-1-benzopyrans analogs as **antiestrogens** having the following molecular structure: ##STR2##

SUMM . . . et al., J. Med. Chem. 32: 1700-1707 (1989) describe the synthesis and biological activities of benzofuran and triarylfuran analogues as **antiestrogens**.

SUMM It is another object of the invention to provide a pure **antiestrogen** for therapeutic use.

SUMM It is another object to provide an **antiestrogen** having good affinity for estrogen receptors, but substantially lacking undesirable agonistic activity regarding these receptors and substantially lacking hormonal activity.

SUMM . . . in the treatment of estrogen-related diseases. These diseases include, but are not limited to breast cancer, uterine cancer, ovarian cancer, **endometriosis**, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

SUMM . . . of inhibiting the activity of androgens and estrogens, respectively. For example, estrogen activity inhibitors include, but are not limited to **antiestrogens** which block estrogen receptors, thereby making them unavailable to estrogen compounds which could otherwise activate those receptors. Sex steroid activity. . .

DRWD . . . affinity of estradiol, diethylstilbestrol, ICI 164384 (Wakeling, A. E. and Bowler, J., 1987; J. Endocrinol. 112: R7-R110) and EM-142 (an **antiestrogen** having a nonsteroidal nucleus and synthesized in example 1, herein) for the rat uterine cytosol receptor (Asselin et al., 1978; . . .

DRWD FIG. 3 is a graph illustrating the antiestrogenic activity of another **antiestrogen** EM 139.

DRWD FIG. 4 is a graph illustrating that the **antiestrogen** which is the subject of FIG. 3 is also a good inhibitor of sex steroid synthesis.

DRWD FIG. 5 is a graph illustrating the **antiestrogen** activity of EM 343 and EM 312, other sex steroid inhibitors of the invention.

DET D When administered systemically, pharmaceuticals of the inventions may be used in the treatment of breast cancer, uterine cancer, ovarian cancer, **endometriosis**, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

DET D Pharmaceutical compositions comprise therapeutically effective amounts of one or more of the sex steroid activity inhibitors (including **antiestrogens**) discussed herein wherein a pharmaceutically acceptable diluent or carrier is included with the active compound(s). The diluent or carrier will. . .

DET D A composition suitable for parenteral administration preferably contains a carrier and an **antiestrogen** in accordance with the invention at a concentration sufficient to introduce from about 1 mg to about 1000 (preferably 5 to 50) mg of the **antiestrogen** per 50 kg of body weight per day. The volume flow will, of course, vary with the concentration at which. . .

DET D After E.sub.2 and/or **antiestrogen** treatment, cells were harvested by addition of 0.5 ml of a pancreatin solution (Sigma) for 5-10 min at 37.degree. C. . .

DET D Set forth below are some flow charm description and illustration of a

number of preferred synthesis schemes for certain preferred **antiestrogens** in accordance with the invention. The steps set forth below are set forth merely by way of example. Those of skill in the art will readily recognize alternative synthetic pathways and variations capable of producing a variety of **antiestrogens** and other sex steroid activity inhibitors in accordance with the invention.

DETD EFFECTIVENESS OF **ANTIESTROGEN** SYNTHESIZED IN EXAMPLE 1

DETD . . . can be seen that EM-142 is only 3 times less potent than 17.beta.-estradiol itself while being more potent than the **antiestrogen** ICI 164384.

DETD EFFICACY OF AN **ANTIESTROGEN** SYNTHESIZED IN ACCORDANCE WITH EXAMPLE 9

DETD . . . Scheme 9 above is an estrogen activity inhibitor. "EM 139" has been tested both for efficacy in acting as an **antiestrogen** by blocking estrogen receptors without substantially activating those receptors (see FIG. 3), and for efficacy in inhibiting 17.beta.-hydroxysteroid dehydrogenase (see. . . .

L11 ANSWER 8 OF 10 USPATFULL

AB Certain steroidal and non-steroidal compounds have been found to inhibit

androgen and estrogen formation. Such inhibition may aid in the reduction of the activity of these hormones and may be useful in the treatment of diseases where, for example, inhibition of androgen or estrogen acitivity is desired. Preferred inhibitors also possess antiestrogenic activity, thus providing the advantage of a double inhibitory action both on estrogen formation and on estrogen action.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 94:99900 USPATFULL

TITLE: Inhibitors of sex steroid biosynthesis and methods for their production and use

INVENTOR(S): Labrie, Fernand, Quebec, Canada

Merand, Yves, Quebec, Canada

PATENT ASSIGNEE(S): Endorecherche, Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5364847	19941115	<--
APPLICATION INFO.:	US 1992-966112	19921022 (7)	
DISCLAIMER DATE:	20100420		
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1989-322154, filed on 10 Mar 1989, now abandoned		
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Cintins, Marianne M.		
ASSISTANT EXAMINER:	Jordan, Kimberly R.		
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	3 Drawing Figure(s); 3 Drawing Page(s)		
LINE COUNT:	1504		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5364847 19941115

<--

DETD . . . sex steroid formation and to act as antagonists to sex steroid activity by blocking sex steroid receptors. For example, preferred **antiestrogens** which also act as inhibitors of estrogen formation include, but are not limited to, N-butyl, N-methyl-11-(16.alpha.-chloro-3',17'.beta.-dihydroxy estra-1',3',5'(10')-trien-7'.alpha.-yl) undecanamide ("EM 139"),. . . . are not limited to, malignant as well as non-malignant steroid-sensitive diseases, especially breast cancer, prostate cancer, ovarian cancer, endometrial cancer, **endometriosis**, uterine leiomyomata, precocious puberty, hirsutism, acne, seborrhea, androgenic alopecia, benign prostatic hyperplasia, sexual deviants as well as for male and. . . . at a step

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preceding steroid receptors, thus acting prior to and in addition to the action of steroid antagonists (e.g. **antiestrogens** or antiandrogens).

DETD Such compounds administered at appropriate doses are of value in all conditions where **antiestrogens** and antiandrogens are beneficial. In particular, this approach is of value in breast cancer, prostate cancer, endometrial cancer, ovarian cancer, **endometriosis**, benign prostatic hyperplasia, precocious puberty, hirsutism, acne, seborrhea, androgenic alopecia, menstrual disorders and as male and female contraceptive as well. . . .

DETD . . . dosage of the above-described compound (multi sex hormone blocker) are the same as in intact patients or patients receiving an **LHRH agonist** or **antagonist**.

DETD The composition may contain, in addition to the steroid and/or nonsteroidal derivatives of the invention, other **antiestrogens** and/or antiandrogens and/or enzymatic inhibitors and/or inhibitors of ACTH and/or growth hormone and/or prolactin secretion.

DETD . . . phase was washed with water, dried on anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue included two important **antiestrogens** which were separated by chromatography on silica gel and eluted with a mixture of EtOAc/hexane (4:6 v/v) to give: N-butyl, . . .

L11 ANSWER 9 OF 10 USPATFULL

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 94:97559 USPATFULL
 TITLE: Methods of treating or preventing breast or endometrial
 cancer with low dose non-masculinizing androgenic compounds
 INVENTOR(S): Labrie, Fernand, Quebec, Canada
 PATENT ASSIGNEE(S): Endorecherche, Inc., Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5362720	19941108	<--
APPLICATION INFO.:	US 1993-15083	19930208 (8)	
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1991-724532, filed on 28 Jun 1991, now abandoned		
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Nutter, Nathan M.		
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen		
NUMBER OF CLAIMS:	30		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	1452		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			
PI	US 5362720	19941108	<--
AB	A method of treatment or prevention of breast and endometrial cancer, osteoporosis and endometriosis in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and. . .		
SUMM	This invention relates to a method for treating or preventing breast and		

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endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to kits containing active ingredients. . . .

SUMM . . . for breast and endometrial cancer as well as for the prevention and treatment of bone loss and for treatment of **endometriosis**. The main approaches for the treatment of already developed breast cancer are related to the inhibition of estrogen action and/or. . . .

SUMM . . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing

Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum estrogens to castrated levels. . . .

SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20: 1381, 1984; Manni et al., Endocrinol. Rev. 7: 89-94, 1986). Beneficial effects of treatment with **LHRH agonists** have also been observed in postmenopausal women (Nicholson et al., J. Steroid Biochem. 23: 843-848, 1985).

SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.

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Antiestrogens, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . . .

SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa. . . .

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SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

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SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . of said androgenic steroid described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for all purposes which are enhanced by administering androgens or otherwise. . . .

DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . . .

DETD . . . prevent other signs and symptoms of menopause. In women, when estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . . .

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DETD . . . the above therapy using the described regimen, tumor growth of breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . . .

L11 ANSWER 10 OF 10 USPATFULL

AB Novel compounds for the inhibition of sex steroid activity for the treatment of both androgen-related and estrogen-related diseases

include

for example 15- and 16-halo substituted compounds such as: ##STR1## The compounds are characterized by an estrogenic nucleus substituted with a substituent of the formula --R.sup.1 [B--R.sup.2 --].sub.x L--G wherein

at least one of L and G is a polar moiety distanced from a ring carbon of the estrogenic nucleus by a least three intervening atoms:

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x is an integer from 0-6;

R.sup.1 and R.sup.2 are independently either absent or selected from the group consisting of straight- or branched-chain alkylene, straight- or branched-chain alkynylene, straight- or branched-chain alkenylene, phenylene, and fluoro-substituted analogs of the foregoing; and

B is either absent or selected from the group consisting of --O--, --Se--, --SO--, --SO₂--, --NR.sup.3--, --SiR.sup.3.sub.2--, --CR.sup.3 OR.sup.3--, NR.sup.3 CO--, NR.sup.3 CS--, --CONR.sup.3--, CSNR.sup.3--, --COO--, --COS--, --SCO--, --CSS--, --SCS--, --OCO-- and phenylene (R.sup.3 being hydrogen or lower alkyl).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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TITLE: Estrogen nucleus derivatives for use in inhibition of sex steroid activity
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.			
PI	US 5204337	19930420	<--
SUMM	This invention relates to novel inhibitors of sex steroid activity such as antiestrogen compounds having effective antagonistic capability while substantially lacking agonistic effects. More particularly, certain preferred embodiments of the invention relate to. . .		
SUMM	. . . the amount of sex steroid available to act at these sites. For example, alternative or concurrent therapy to administration of antiestrogens could involve attempts to block the production of estrogens (e.g. by ovariectomy) such that less is available to activate receptor. . .		
SUMM	There is, therefore, a need in the art for antiestrogens which effectively block estrogen receptors with minimal or no agonistic effect. Numerous compounds have been tried in the art with mixed results. Known antiestrogens continue to exhibit undesirable agonistic activity. See, for instance, Wakeling and Bowler, "Steroidal Pure Antioestrogens ", J. Endocrinol. (1987) 112, R7-R10. The net effectiveness of prior art compounds is determined by the balance between their agonistic. . .		
SUMM	In U.S. Pat. No. 4,094,994, it is disclosed that the use of certain		

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antiestrogens may inhibit certain human breast tumor cells.

SUMM H. Mooridsen et al., Cancer Treatment Review 5, 131-141, (1978), discloses that Tamoxiphen, an **antiestrogen**, is effective in remission of advanced breast cancer in about 30 percent of the women patients treated.

SUMM The combined used of the **antiestrogen** Tamoxiphen and a luteinizing hormone-releasing hormone agonist, Buserelin, is also known for treatment of breast cancer. See, for instance, Klijn. . . .

SUMM . . . male animals including humans whose testicular hormonal secretions are blocked by surgical or chemical means, e.g., by use of an

LHRH agonist, e.g., [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]LHRH ethylamide. The treatment includes administering an antiandrogen, e.g., flutamide in association with at least one inhibitor. . . .

SUMM U.S. Pat. No. 4,472,382 relates to a method of treating prostate cancer using the combination of an antiandrogen and an **LHRH agonist**.

SUMM It is another object of the invention to provide a steroidal pure **antiestrogen** for therapeutic use.

SUMM It is another object to provide an **antiestrogen** having good affinity for estrogen receptors, but substantially lacking undesirable agonistic activity regarding these receptors and substantially lacking hormonal activity.

SUMM . . . in the treatment of estrogen-related diseases. These diseases include, but are not limited to, breast cancer, uterine cancer, ovarian cancer, **endometriosis**, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

SUMM . . . also be useful in male contraception. Estrogen-related diseases include but are not limited to breast cancer, uterine cancer, ovarian cancer, **endometriosis**, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

SUMM . . . of inhibiting the activity of androgens and estrogens, respectively. For example, estrogen activity inhibitors include, but are not limited to **antiestrogens** which block estrogen receptors, thereby making them unavailable to estrogen compounds which could otherwise activate those receptors. Sex steroid activity. . . .

DRWD FIG. 1 is a graph illustrating the antiestrogenic activity of one preferred **antiestrogen** of the invention.

DRWD FIG. 2 is a graph illustrating that the **antiestrogen** which is the subject of FIG. 1 is also a good inhibitor of sex steroid synthesis.

DETD Efficacy of an **antiestrogen** synthesized in accordance with Example 1

DETD . . . Scheme 2 above is an estrogen activity inhibitor. "EM 139" has been tested both for efficacy in acting as an **antiestrogen** by blocking estrogen receptors without substantially activating those receptors, (see FIG. 1 and explanation below) and for efficacy in inhibiting. . . .

DETD . . . adult female ovariectomized Balb/c mice (body weight=19-20 g) sacrificed five days after ovariectomy. Ovariectomized mice injected with estradiol and no **antiestrogen** had a resultant uterine weight as shown by the shaded area designated "OVX +E.sub.2" in FIG. 1.

1. The baseline uterine weight for a control group of ovariectomized mice injected with neither estradiol nor **antiestrogen** is represented in FIG. 1 by "OVX". The **antiestrogen** "EM 139", and estradiol dissolved in ethanol were injected subcutaneously in the appropriate test groups in a solution of 0.9%. . . .